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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,509	06/25/2001	Fritz Grunert	24741-1523	9439

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,509	GRUNERT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-12,15-17 and 19-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-12,15-17 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/16/04 has been entered. Applicant's amendment filed concurrently with the RCE submission has also been entered. Claim 1 has been amended and new claims 19-22 have been added. Claims 1-6, 8-12, 15-17, and 19-22 are pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of previously pending claims 1-6, 8-12, and 15-17 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained in part and newly applied to pending claims 1-6, 8-12, 15-17, and 19-22.

The applicant has amended claim 1 step (b) to recite, "...wherein the expression vector employed for the genetic, is the same as that used in vitro for producing the target polypeptide in step(a)..". The claim as amended is missing the word "immunization" after the word genetic. It is unclear whether the applicant intended to delete this word, or whether it is a typographical error. This rejection can be overcome by re-inserting the word "immunization" after the word genetic. Please note as well that in claim 1 step (b), there is a lack of antecedent basis for , "the target polypeptide in step (a)". Step(a) does not recite a "target" polypeptide. Deleting the word "target" would overcome this aspect of the rejection.

The applicant's amendment to claim 1 step (c) to recite, ".. the antibodies that are formed in step (b) are removed from the animal in the form of serum, or following cell fusion, from hybridoma supernatants and then incubated with mammalian host cells from step (a) to obtain binding of the transiently expressed polypeptides on their surfaces" has resulted in a new grounds of rejection. The claim as newly amended is confusing and indefinite. As written, it is unclear as to what the transiently expressed polypeptides are binding. Amendment of the claim to read, ".... are then incubated with mammalian host cells from step (a) to obtain binding of said antibodies to the transiently expressed polypeptides on the cell surfaces..", would overcome this element of the rejection.

Since claims 2-6, 8-12, 15-17, and 19-21 all ultimately depend on claim 1, they are likewise rejected based on the indefiniteness of claim 1.

Claim 16 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. Based on the amendment to claim 1, the limitations of claim 16 are now confusing and indefinite. Claim 16 recites, "The process according to claim 1, wherein the antibody which is reacted with the expressed polypeptide in step (c) is released by elution.". Step (c) of claim 1 no longer recites reacting the antibody with an expressed polypeptide. Since claim 1 is also rejected above for indefiniteness based on step (c), it is suggested that claim 16 be amended concurrently with claim 1.

Claim 22 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. New claim 22 is confusing in that it is unclear when step (c) occurs in relation to the other steps. As such, it is unclear whether the host cell which transiently expresses the polypeptide is incubated with the solid phase matrix which has already bound antibody or simply with the solid phase matrix itself.

Claim Rejections - 35 USC § 103

The rejection of claims 1-6, 8-12, and 15-17 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,773,293 (6/30/98), hereafter referred to as Kilgannon et al., in view of U.S. Patent No. 5,736,524 (4/7/98), hereafter referred to as Content et al., and further in view of Letesson et al. (1997) Clin. Diag. Lab. Immunol., Vol. 4, 556-564 and Whitehorn et al. (1995) Bio/Technology, Vol. 13, 1215-1219, is withdrawn in view of applicant's amendments to claim 1.

Applicant's amendment to claim 1 and addition of new claim 22 has resulted in the following new grounds of rejection under 35 U.S.C. 103(a).

Claims 1-6, 8-12, 15-17, and 19-22 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Forster et al. (1993) Biochem. Biophys. Res. Comm., Vol. 196 (3), 1496-1503, in view of U.S. Patent No. 5,736,524 (4/7/98), hereafter referred to as Content et al., and further in view of Letesson et al. (1997) Clin. Diag. Lab. Immunol., Vol. 4, 556-564 and Whitehorn et al. (1995) Bio/Technology, Vol. 13, 1215-1219. The applicant claims processes for producing antibodies which react specifically with a polypeptide comprising immunizing an animal with a DNA encoding the polypeptide linked to a detection signal such that antibodies are formed and reacting the antibodies with cells transfected with the same DNA encoding the polypeptide. The applicant further claims said processes wherein the signal is an hexa-histidine tag sequence or GPI, wherein the DNA sequence encoding the polypeptide is operatively linked to the CMV promoter, or wherein a cytokine expression vector is co-administered to the animal along with the DNA encoding the polypeptide. In addition, the applicant claims said processes wherein the antibody and/or cells are incubated with a solid matrix, and wherein the antibody bound to the polypeptide is detected by an anti-antibody and is subsequently released by elution.

Forster et al. teaches solid phase whole cell ELISA assay for detecting antibodies which bind to a specific protein comprising 1) immunizing a host with cells transfected with an expression vector which expresses a fusion protein comprising human BLR1 and a MYC epitope tag under operative control of the CMV promoter, 2) removing antibody producing cells from the host and making hybridomas, 3) binding antigen specific antibodies by incubating the

hybridoma supernatant with plates coated with the same transfected cells which were used for the immunization, and 4) detecting antibody binding by incubating the plates with labeled anti-IgG and labeled anti-MYC antibodies (Forster et al., pages 1497-1498). Forster et al. further teaches using this cell ELISA method to screen for antibodies specific to any cloned protein which can be overexpressed in eukaryotic cells (Forster et al., page 1503).

While Forster et al. teaches that the detection signal in the fusion protein is a MYC epitope tag, the use of epitope tags such as hexa-histidine or GPI residues was well known at the time of filing as evidenced by the teachings of Letesson et al. and Whitehorn et al.. Letesson et al. teaches recombinant fusion proteins containing a hexa-histidine peptide at the C-terminus useful for detecting/purifying the fusion protein and for coating microtiter plates in order to detect antibody binding to the fusion protein (Letesson et al., pages 557-558). Whitehorn et al. teaches recombinant fusion protein containing a GPI anchor at the C-terminus useful for detecting/purifying the fusion protein following cleavage of the GPI anchor (Whitehorn, page 1215). Thus, based on the motivation to use various epitope tags to detect fusion protein expression and the use of fusion proteins containing MYC, hexahistidine tags, or GPI residues, in immunoassays, it would have been *prima facie* obvious to the skilled artisan to substitute other well-known detection signals such as hexahistidine or GPI for MYC in the methods of making and using fusion proteins taught by Forster et al. Further, based on the high level of skill in molecular biology, the skilled artisan would have had a reasonable expectation of success in modifying the vector taught by Forster et al. to include a hexahistidine epitope tag or a GPI tag.

While Forster et al. teaches the immunization of mammalian hosts with recombinant cells which have been transfected with an expression vector encoding a fusion protein, Forster et al.

does not teach the direct injection of DNA encoding the polypeptide into mice in order to generate antibodies. Content et al. supplements Forster et al. by teaching the generation of antibodies *in vivo* in mice by direct administration of a DNA plasmid vector encoding a polypeptide of interest (Content et al., columns 10-13 and 17). The DNA plasmid vector can be administered by direct intramuscular injection or by a jet injector using gold microprojectiles coated with the DNA (Content et al. column 2). Please note that the jet injector is commonly referred to as a "gene gun". Content et al. further teaches that vectors encoding a polypeptide operatively linked to the CMV promoter and BGH transcriptional termination sequence (polyA sequence) can be used not only to express the polypeptide *in vivo*, but also to produce the protein in cells *in vitro* (Content et al., columns 10-14). In addition, Content et al. teaches the enhancement of immunization by the co-administration of DNA encoding the polypeptide and DNA encoding immunostimulatory cytokines (Content et al., column 9). Finally, Content et al. provides motivation to use eukaryotic vectors instead of protein to generate antigen specific antibodies *in vivo*. Content teaches that its better to immunize with a gene rather than a gene product for the following reasons: 1) the simplicity with which native or nearly native antigen can be presented to the immune system using genetic immunization, and 2) the fact that mammalian proteins expressed recombinantly in bacteria, yeast, or even mammalian cells often require extensive treatment to insure appropriate antigenicity (column 9, lines 60-66). In view of the motivation provided by Content et al. to use a gene rather than a gene product or cell to produce antibodies *in vivo*, it would have been *prima facie* obvious to the skilled artisan at the time of filing to directly inject the expression vector encoding the fusion protein taught by Forster et al. *in vivo* rather than the cells transfected with the expression vector to produce

antibodies. Further, based on the high level of skill in the art of molecular biology and the specific teachings in Foster and Content as to mammalian expression vectors useful for both producing antibodies *in vivo* and producing protein in mammalian cells *in vitro*, the skilled artisan would have had a reasonable expectation of success in modifying the expression vectors taught by Content et al. to include the polypeptide fusion protein taught by Forster et al., and in using the modified vector to generate antibodies *in vivo* and in producing protein in mammalian cells *in vitro*.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER